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GUARDANT HEALTH, INC.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

GUARDANT HEALTH, INC.,

Plaintiff/Counterclaim-
Defendant,

vs.

NATERA, INC.,

Defendant/Counterclaim-
Plaintiff.

Case No. 3:21-cv-04062-EMC

**GUARDANT’S *DAUBERT* MOTION TO
EXCLUDE UNRELIABLE EXPERT
TESTIMONY FROM DR. HOWARD
HOCHSTER REGARDING COBRA
STUDY**

Pretrial Hearing Date: October 15, 2024
Trial Date: November 12, 2024

1 **TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD HEREIN:**

2 PLEASE TAKE NOTICE that on July 26, 2024, at 10:30 a.m. (Pacific), or as soon
3 thereafter as this matter may be heard in Courtroom 5 of the United States District Court for the
4 Northern District of California, San Francisco Division, located in the United States Courthouse at
5 450 Golden Gate Avenue, San Francisco, California, 94102, the Honorable Edward M. Chen
6 presiding, Plaintiff/Counter Defendant Guardant Health, Inc. (“Guardant”), by and through its
7 attorneys, will hereby respectfully move the Court for an Order excluding testimony offered by
8 Natera, Inc.’s putative expert Howard S. Hochster, M.D., concerning the COBRA study pursuant
9 to FED. R. EVID. 702, 703, and 403.

10 This motion is made upon this notice, the attached memorandum of points and authorities,
11 the declaration of Saul Perloff and exhibits thereto, all records, papers, and pleadings on file in this
12 action, and all further evidence as may be presented prior to or after the filing of the motion.

13 Dated: July 1, 2024

SHEARMAN & STERLING, LLP

14 By: /s/Saul Perloff
15 Saul Perloff

16 Attorney for Plaintiff/Counterclaim Defendant
17 GUARDANT HEALTH, INC.
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MEMORANDUM OF POINTS AND AUTHORITIES

I. INTRODUCTION

Dr. Hochster's opinions about the COBRA study should be excluded for three reasons. *First*, he is unqualified to opine about statistical analysis, [REDACTED]

[REDACTED] Tr. of Dep. of H. Hochster Ex. A (Jun. 18, 2024) ("COBRA Dep.") at 68:17-19.¹ Dr. Hochster nevertheless offers opinions about COBRA's statistical analysis, including a gross misapplication of the p-value, a cornerstone of statistics and a critical concept underlying his opinions.

Second, Dr. Hochster's "methodology" lacks scientific reliability. He undertook no independent data analysis, and never assessed the untested assumptions underlying COBRA's futility analysis. Worse still, he baldly speculates about Natera's hypothetical performance.

Third, any benefit from Dr. Hochster's non-expert expert testimony is eclipsed by the real danger of unfair prejudice. COBRA is the *only* issue which has been the subject of fact discovery over the last two years, and it is likely the jury will misunderstand its limited relevance to any issue in this case. This danger is magnified if Natera offers Dr. Hochster's flimsy opinions—which fall outside of COBRA's potential relevance—with a medical doctor's imprimatur.

In the end, Dr. Hochster's COBRA opinions, for all their sound and fury, signify nothing. Under *Daubert* and Rules 702 and 703, the Court should exclude Dr. Hochster's COBRA opinions because they are unreliable. The Court should also exclude his opinions under Rule 403 because their probative value (if any) is outweighed by the undue prejudice to Guardant.

II. FACTUAL BACKGROUND

A. The COBRA Study

While detection of ctDNA through assays like Reveal and Signatera is strongly associated with CRC recurrence, there is no consensus a positive ctDNA test alone warrants chemotherapy. Ex. B (Hochster Suppl. Ex. 3) ("COBRA Protocol"); Ex. 3112 ("Morris Presentation") slide 2; Parikh Rebuttal Rept. ¶ 25. The COBRA study, NRG-GI005, was to test whether, "for patients

¹ All exhibits are attached to the Declaration of Saul Perloff, submitted herewith.

1 whose Stage II colon cancer has been resected and who have no traditional high-risk features, a
2 positive ctDNA status may identify those who will benefit from adjuvant chemotherapy.” *Id.*

3 COBRA “was sponsored by NRG Oncology and began enrolling patients in December
4 2019,” Parikh Rebuttal Rept. ¶ 33. Guardant responded to NRG’s Request for Application on
5 March 1, 2017, Ex. C (GHI00063309), and NRG selected Reveal for use in COBRA. Morris
6 Presentation, slide 5. [REDACTED] Ex. D, Dep. of A. Aleshin (May
7 29, 2024) (“COBRA Dep.”) 56:11-13.

8 COBRA randomized patients into Arms 1 (observation) and 2 (adjuvant chemotherapy).
9 COBRA Protocol. COBRA was to have primary endpoints at the end of Phase II (clearance of
10 ctDNA with chemotherapy) and Phase III (recurrence-free survival for ctDNA-detected patients).
11 *Id.* “[E]valuating the clinical performance (e.g., the sensitivity, specificity, PPV or NPV) of the
12 Reveal assay was not a stated objective of the COBRA Study.” Parikh Rebuttal Rept. ¶ 35.

13 The COBRA study’s Phase II endpoint’s null hypothesis was that there would be no
14 difference in clearance rates between Arm 1 and 2 patients. Parikh Rebuttal Rept. ¶ 45. In testing
15 this hypothesis, COBRA’s design made several presumptions, including that the baseline ctDNA-
16 detected rate would be 5.45%, that only 10% of baseline ctDNA+ patients in Arm 1 (observation)
17 would clear ctDNA at six months, while 60% of baseline ctDNA+ patients in Arm 2
18 (chemotherapy) would clear at six months. *See* Morris Presentation slide 6. COBRA required
19 collection of the six-month sample *during* chemotherapy for Arm 2 patients. *Id.* slide 3.

20 Launched shortly before COVID struck, patient enrollment in COBRA was slow, and only
21 635 patients accrued before the study was discontinued. Morris Presentation, slide 9. After
22 randomization, seven of the first sixteen baseline ctDNA+ patients were in Arm 1 (observation),
23 while nine were in Arm 2 (chemotherapy). At six months, three of the seven Arm 1 patients cleared
24 (did not have ctDNA detected), for a 43% clearance rate (95% confidential interval, or “CI,” of 10-
25 82%). Ex. E Final Abstract (Hochster Suppl. Rept. Ex. 2). One of the nine Arm 2 patients cleared,
26 for an 11% clearance rate (95% CI of 0.3-48%). *Id.* Notably, one of the Arm 2 patients declined to
27 receive chemotherapy, but was nevertheless included in Arm 2. *Id.*

B. COBRA was halted following results premised on untested assumptions

Based on Arm 1's 43% vs. Arm 2's 11% clearance rates (which was contrary to the study's assumptions of 10% and 60% clearance rates respectively), the null hypothesis—there was no difference in clearance rates between the Arms—could not be rejected. Morris Presentation slide 7 (“Because the 1-sided Fisher’s Exact Test yields $p = 0.98$ exceeded 0.35, the null hypothesis was not rejected, and the decision rule called for early stopping due to futility.”)² This analysis was not based on any clinical outcome data, which remain unknown. Parikh Rebuttal Rept. ¶ 67.

Based on these few interim data, NRG chose to discontinue the COBRA study. Ex. 3108 (NRG Dear Colleague Letter (Aug. 30, 2023)). As NRG observed, patients participating in the COBRA study had been warned that “‘false positive’ and ‘false negative’ test results were possible, so this is not an unanticipated risk; nor is it a risk unique to this diagnostic test.” *Id.* However, NRG’s Letter went on to state it had “been informed by our diagnostic partner that a greater than anticipated number of participants may have been ‘false positives’, i.e., designated ctDNA+ incorrectly. While this was a recognized potential risk of the study, this rate is higher than we had expected.” *Id.* NRG further stated that: “The higher-than-expected ‘false positive’ rate resulted in the trial not passing the interim analysis and, as such, the trial will be closed to accrual.” *Id.*

Guardant had not advised NRG that the Phase II results were “false positives.” Rather, it explained that in 2022 it “

Ex. H (July 26, 2023 Guardant letter).

² COBRA’s Phase II interim analysis was not “truly a ‘futility’ analysis” “because it did not refer to the probability that the phase III portion would be successful, given the results of the phase II; it merely summarized the results of the first 16 patients, without considering the possibility that things might turn out differently once the full trial was enrolled.” Ex. F, Heitjan Rebuttal Rept. ¶ 38.

Ex. G, Sept. 13, 2023 email from P. Boland to H. Hochster (“Preliminary Abstract”).

Because there are no clinical outcome data available for the sixteen patients involved in the COBRA futility analysis, there is no way to know if any of the ctDNA+ calls at either baseline or during the six-month draw in either Arm 1 or 2 were true or false positives. And while the discontinuation of the COBRA study was disappointing, it now is plain that assumptions built into the study’s design and futility analysis, developed between 2017 and 2019 before much of the scholarship informing ctDNA assays was conducted and published, were deeply flawed:

- COBRA took the six-month blood samples in Arm 2 *during* chemotherapy, contrary to current recommendations.
- COBRA assumed only 10% of the Arm 1 baseline ctDNA+ patients would clear, though data now show that 12-20% of untreated patients may self-clear, while others may undergo transitory clearance, wherein ctDNA positive patients become negative for a time, only to again test ctDNA+ with more follow-up.
- COBRA also assumed that 60% of baseline ctDNA+ patients in Arm 2 would clear, though studies show a wide range of clearance following chemotherapy, from as low as 16.7 and 20%. Indeed, Natera’s Reinert study on Signatera showed only a 30% clearance rate.
- The study design failed to account for the impact of the very low recurrence rate in Stage IIA CRC (10% or less), in light of the known analytical specificity of ctDNA assays—which for the L1.2 iteration of Reveal was about 96%. But the COBRA design appears to have assumed a perfect analytical specificity despite known limitations.

Notably, using [REDACTED], COBRA’s “futility” analysis would not have triggered discontinuation. *See* Preliminary Abstract. But these data—and the alternative futility analysis outcome—were not reported in the Final Abstract.

C. Natera and Dr. Hochster concealed his knowledge of and emails about COBRA

On January 31, 2024, four-and-a-half months after receiving the preliminary COBRA abstract from Dr. Boland, Dr. Hochster issued his Suppl. Rept. In his Suppl. Rept., Dr. Hochster relied on the COBRA study’s interim data on 16 patients, with no clinical outcome data, to opine:

1 “the Reveal test did not work as Guardant advertised”;

2 “Reveal only has a 2% chance of accurately predicting DNA clearance”;

3 “Reveal was not performing as reported by Guardant and Parikh”;

4 “the failure of [the COBRA study] is unheard of and will have tremendous and long-
5 lasting impacts on the field”; and

6 “when battle-tested in a real-world setting via a prospective, randomized trial like
7 COBRA, conducted by an independent sponsor, with no room for manipulation, the
8 true performance of Reveal, as exposed, is too prone to aberrant results, cannot meet
9 expectations, and is not on par with tumor-informed tests.”

10 Hochster Supp. Rep. ¶¶ 34, 35, 46; *see also* Amendment at ¶¶ 6-7 (claiming [REDACTED])

11 [REDACTED]). At his
12 deposition he confirmed that these opinions were not based on any independent analysis of the
13 COBRA data, and that he never questioned the COBRA study’s underlying assumptions.

14 In denying Guardant’s motion to strike, the Court held COBRA was potentially relevant as
15 to several issues, including the “cap” on corrective advertising damages. Dkt. 493 at 12. The Court
16 continued trial (now to begin Nov. 12, 2024, Dkt. 557) and allowed limited discovery on COBRA.

17 In its Order, the Court also found: “Natera’s delay in submitting Dr. Hochster’s
18 supplemental report was substantially justified” based on Natera’s representations the data were
19 first available “on January 16, 2024.” *Id.* at 5. But Dr. Hochster in fact [REDACTED]

20 [REDACTED]
21 Hochster COBRA Dep. 21:13-20 & 22:11-18; *id.* at 215:11-25 ([REDACTED])

22 In response to Guardant’s subpoena, and following an order compelling production, Dkt.
23 515, Dr. Hochster produced 11 documents comprising 41 pages. In response to Guardant’s motion
24 to compel, Natera’s counsel represented to the Court that Dr. Hochster sent *no* emails about
25 COBRA, and had searched his emails—twice—to confirm he had no documents. Dkt. 510; Tr. of
26 Hrg. (Apr. 4, 2024) at 6:4-7:23. But through a subpoena to Dr. Hochster’s employer, Rutgers
27 University, Guardant obtained scores of email communications between Dr. Hochster and, for
28 example, Natera’s Chief Medical Officer Dr. Minetta Liu, who directed him to “connect the dots”

1 between Natera and NRG's leadership. Ex. 3109.

2 Rutgers ultimately produced more than 75 of Dr. Hochster's emails (comprising over 500
3 pages). Rutgers' production shows that, immediately after NRG announced its decision to
4 discontinue COBRA, Dr. Hochster repeatedly denigrated Guardant and Reveal in a series of emails
5 to his colleagues, the COBRA study's principal investigator, and NRG's leadership, and acted as
6 Natera's "liaison" with NRG to substitute Signatera for Reveal in COBRA. These third-party
7 documents also show that Dr. Hochster consistently failed to disclose his significant financial
8 relationship with Natera, and his service as a litigation expert, when advocating for Natera with his
9 colleagues, Dr. Morris, and NRG about COBRA.³

10 **III. STATEMENT OF THE ISSUES TO BE DECIDED**

11 Whether the Court should exclude from trial Dr. Hochster's COBRA opinions as set forth
12 in his Suppl. Rept. and Amendment because:

- 13 1. He is unqualified to offer his opinions on the statistical impact of the COBRA data;
- 14 2. He failed to employ a reliable methodology in forming his opinions; and
- 15 3. The undue prejudice to Guardant exceeds the probative value of his opinions.

16 **IV. LEGAL STANDARD**

17 A witness qualified as an expert in "scientific" knowledge may offer opinion testify if:

- 18 (a) the expert's scientific, technical, or other specialized knowledge will help the trier
19 of fact to understand the evidence or to determine a fact in issue;
- 20 (b) the testimony is based on sufficient facts or data;
- 21 (c) the testimony is the product of reliable principles and methods; and
- 22 (d) the expert has reliably applied the principles and methods to the facts of the case.

23 FED. R. EVID. 702. Rule "702 tasks a district judge with 'ensuring that an expert's testimony both
24 rests on a reliable foundation and is relevant to the task at hand.'" Dkt. 328 at 2 (quoting *Daubert*
25 *v. Merrell Dow Pharma., Inc.*, 509 U.S. 579, 597 (1993)). To be "reliable," testimony must be
26 grounded in the methods and procedures of science and based on "more than subjective belief or
27 unsupported speculation." *Daubert*, 509 U.S. at 590.

28 ³ The scope and nature of Natera's and Dr. Hochster's misrepresentations to the Court are serious,
and Guardant is considering the most appropriate means of presenting these issues for the Court's
full consideration.

V. ARGUMENT

A. Dr. Hochster is unqualified to offer his statistical opinions

An expert who admits “he has no expertise in statistical analysis” should not be allowed to offer opinions that rely on such expertise. *Lewert v. Boiron, Inc.*, 212 F. Supp. 3d 917, 936 (C.D. Cal. 2016) (“Given this admission, Dr. DuMont is not qualified to render an opinion that the Ferley and Papp studies are ‘reliable’”), *aff’d*, 742 Fed. Appx. 282 (9th Cir. 2018); *cf. Edwards Lifesci. Corp. v. Meril Life Scis. Pvt. Ltd.*, No. 19-cv-06593, 2022 WL 254348, at *8 n.4 (N.D. Cal. Jan. 27, 2022) (noting lack of sufficient showing that cardiologist was qualified to offer testimony on biostatistics).

Despite his lack of qualifications, Dr. Hochster purports to offer wildly off-base statistical opinions on COBRA. For example, he inaptly declares: “A ‘p-value’ is a statistical measurement used to indicate the statistical significance of the observed differences between two groups. The smaller the p-value, the more likely there is a true difference between the two groups.” Hochster Suppl. Rept. ¶ 21. Dr. Hochster’s “first sentence is circular; the second is incorrect.” Heitjan Rebuttal Rept. ¶ 25. A “P value is ‘the probability of obtaining by chance a result at least as extreme as that observed, even when the null hypothesis is true and no real difference exists’” *A.T. v. Sec. of Health and Hum. Servs.*, No. 16-393, 2021 WL 6495241, at *22, n.26 (U.S. Ct. Fed. Claims Jan. 13, 2022) (quoting Dorland’s Med. Dictionary Online); Heitjan Rebuttal Rept. ¶ 25 (same).

As applied in a statistical analysis to a null hypothesis, “you assume true the hypothesis that you are trying to disprove, in this case that the clearance rate on assay-directed therapy is no greater than the clearance rate on standard of care.” Heitjan Rebuttal Rept. ¶ 25. If the data are inconsistent with the null hypothesis, “you declare the hypothesis disproven.” *Id.*

The proper interpretation of a small p-value is thus that either a) there actually is a difference between the groups, or b) there is no difference, but we have observed the rare data set where the groups appear to be different. The proper interpretation of a large p-value is that either a) there is no difference between the groups, or b) there is a difference, but we have observed the rare data set where the groups do not appear to be different.

Id. But as a core statistical principle, “[t]he p-value does not measure the ‘likelihood’ of a true difference between the groups.” *Id.* Thus, in COBRA, the p-value results did not allow the investigators to reject the null hypothesis “that the clearance rate on test-directed therapy is no greater than the clearance rate on standard of care in this cohort.” *Id.* ¶ 22.

Based on his lack of understanding, Dr. Hochster nevertheless would tell the jury that:

From a statistical point of view, the COBRA study data showed that the Reveal test did not work as Guardant advertised either. As discussed earlier, the p-value goal for this Phase II endpoint analysis is $p < 0.35$, which is already significantly more permissive than the usual $p < 0.05$ standard. But Reveal’s performance is so far away from even that lowered standard. The reported p-value is 0.98, which effectively means that, with respect to the endpoint of “ctDNA clearance,” ***Reveal only has a 2% chance of accurately predicting DNA clearance.*** In other words, Reveal was unable to distinguish between positive patients treated with chemotherapy or those observed without chemotherapy.

Hochster Suppl. Rept. ¶ 32 (emphasis added, note omitted). But: “This is not correct; a p-value of 0.98 means that, assuming there is no difference between arms, 98% of the time one would observe a result as extreme or more extreme than what was seen in the data. That is, it merely states that if there is in fact no difference between arms, it is quite likely that one will observe an effect estimate of this size or larger.” Heitjan Rebuttal Rept. ¶ 28. ***“The p-value does not in any sense quantify ‘the chance of accurately predicting DNA clearance.’”*** *Id.* (emphasis added).

This Court’s “exercise of [its] gatekeeping function is critically important ‘to ensure the reliability and relevancy of expert testimony.’” *Jinro Am., Inc. v. Secure Invest., Inc.*, 266 F.3d 993, 1005 (9th Cir. 2001) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). This Court should exercise its “discretion to choose among reasonable means of excluding expertise that is *fausse* and science that is junky.” *Id.* (quoting *Kumho*, 526 U.S. at 159 (Scalia, J., concurring)). Here, Dr. Hochster is entirely unqualified to offer his unsupported statistical opinions to the jury. His opinions would likely mislead and confuse the jury. The Court should exclude them.

B. Dr. Hochster opinions are not based on personal knowledge or any methodology

Under *Daubert*, the focus of the Court’s assessment of the admissibility of expert testimony “must be solely on principles and methodology, not on the conclusions that they generate.” *Daubert*, 509 U.S. 594. “But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.” *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)

Dr. Hochster’s opinions are nothing more than impermissible *ipse dixit*. [REDACTED]
[REDACTED], despite claims he was “very knowledgeable about the COBRA study and Reveal’s performance in the COBRA study.” Hochster Suppl. Rept. ¶ 26; Dkt. 493 at 5 (“Dr. Hochster is personally knowledgeable of the COBRA clinical trial”). Dr. Hochster’s claim to have “monitored” COBRA, Hochster Suppl. Rept. ¶ 11, [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

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[REDACTED]

C. Dr. Hochster failed to consider COBRA's unfounded assumptions and design flaws

Dr. Hochster's lack of analysis and his failure to question any assumptions reflects the

complete absence of any discernable, much less reliable, methodology. Were Dr. Hochster offering a differential diagnosis as to the cause of a patient's cancer, his failure to even consider potential alternative causes would mandate exclusion of his opinion. E.g., *Whisnant v. U.S.*, 274 Fed. Appx. 536, 537 (9th Cir. 2008) ("the expert's differential diagnosis failed to account for possible alternate causes of the plaintiff's symptoms") (citing *Clausen v. M/V New Carissa*, 339 F.3d 1049, 1058 (9th Cir. 2003)). The same result should apply to his opinions on COBRA.

1. COBRA's flawed assumptions about analytical specificity

To begin, Dr. Hochster's contention that COBRA's data "demonstrate that the Reveal test did not work as Guardant and Dr. Parikh reported," Hochster Suppl. Rept. ¶ 28, *id.* ¶¶ 34-35, is not only speculative given the lack of any clinical outcome data, but fundamentally misunderstands how Reveal's high analytical specificity would be expected to perform in a low-recurrence population. Unfortunately, this misunderstanding appears to have been shared by COBRA's designers. See Heitjan Rebuttal Rept. ¶¶ 15-18 & 62-67; Parikh Rebuttal Rept. ¶¶ 53-60.

Guardant targeted Reveal's analytical specificity for 95%, and validated it in a range of 95.9 to 96.7%, Ex. H, Heitjan Rebuttal Rept. ¶ 62 Ex. F, which was very close to its 95.4% clinical specificity (which improved to 100% with a year follow-up) later validated in the Parikh Study. Parikh Rebuttal Rept. ¶¶ 54, 63. But as Drs. Heitjan and Parikh explain, a low recurrence rate in a large population increases the likelihood of potential false positives, even with an extremely high analytical specificity. *Id.* ¶ 57; Heitjan Rebuttal Rept. ¶ 63. In a cohort of 600 patients, with an anticipated recurrence risk of only 10%, one would expect a total of 60 true positives/false negatives (and with a 50% sensitivity, about 30 of each would be anticipated). Of the 540 patients anticipated to not recur, about 5% (or 27 patients) might be false positives. Thus, if the recurrence rate is low, the proportion of true to potential false positives can be close to even. Ex. 3113 (Parikh Presentation) slide 22.

In short, "the supposedly excessive number of 'false positives' in COBRA is a consequence of the study design and the low-risk patient cohort, and not a flaw in Reveal or an indication that 'the Reveal test did not work as Guardant advertised.'" Heitjan Rebuttal Rept. ¶ 67.

2. COBRA's assumptions about recurrence rates were flawed

Two key assumptions underlying COBRA's futility analysis is that only 10% of patients with ctDNA detected at baseline in Arm 1 would clear without treatment, while 60% of patients with ctDNA detected at baseline in Arm 2 would clear with treatment. Morris Presentation slide 8. Neither assumption bears scrutiny in light of actual data.

As reported by Malla *et al*, the range of clearance with chemotherapy spans 16.7% to 67.7%:

Study	Stage	Ability of Adjuvant Therapy to Convert ctDNA-Positive to ctDNA-Negative (% of ctDNA clearance postoperatively)
Reinert et al ²⁵	I-III	3/10 (30)
Parikh et al ¹⁵	I-III	1/6 (16.7)
Tie et al ¹⁶	II	3/6 (50)
Tie et al ¹⁷	III	5/20 (25)
Henriksen et al ¹⁸	III	4/20 (20)
Tie et al ²⁰	IV	3/11 (27.3)
Kotaka et al ²⁴	I-IV	65/96 (67.7)

Ex. 3102; Hochster COBRA Dep. at 116:18-24 (Reinert study data showed only 30% clearance).

On the other hand, recent studies reflect spontaneous self-clearance for untreated patients higher than COBRA's assumed 10%, including 12% in the GALAXY trial, and 20% in the DYNAMIC trial. Ex. H (collecting studies). Another factor the COBRA design did not account for is "transient clearance," wherein a patient temporarily tests ctDNA negative, only to test ctDNA-positive thereafter (and often recur). Parikh Presentation slide 13; Hochster COBRA Dep. at 126:23-127:5 ("Transient clearance' is a situation where a patient who originally presented ctDNA-positive shows a ctDNA-negative result, only to then become ctDNA-positive later.")

In fairness to the COBRA designers, there had been very little research on the phenomenon of ctDNA clearance published in 2019, while today there is far more. Hochster COBRA Dep. 131:19-25. Dr. Hochster, however, cannot rely on such ignorance. COBRA's assumptions that 10% of untreated patients would clear, while 60% of treated patients would clear, are not well supported by current studies, but Dr. Hochster based his opinions and criticisms of Reveal on their accuracy.

Dr. Hochster's acquiescence in untested assumptions is all the more significant because the COBRA data set is small. "One problem with small studies — even those whose outcome is statistically significant — is that their results can be sensitive to modest changes in the data,

1 implying that although the analysis turned out one way, it could easily have turned out another.”

2 Heitjan Rebuttal Rept. ¶ 46. Here, the number of patient data points is so small, the confidence

3 intervals for the futility data overlap. Final Abstract (“3 of 7 pts (43%, 95% CI 10-82%) in the

4 control arm and in 1 of 9 pts (11%, 95% CI 0.3-48%) in in the experimental arm after chemotherapy

5 ($p=.98$).”) In other words, “the ctDNA outcomes among patients on assay-directed therapy (i.e.,

6 clearance in only 1 of 9 patients) are not as discouraging as they may first appear,” and “the ctDNA

7 outcomes among patients on standard-of-care therapy (i.e., clearance in 3 of 7 patients) are not as

8 surprising as they first appear.” Heitjan Rebuttal Rept. ¶¶ 54-55 (observing: “this data set does not

9 exclude clearance rates as low as 10%, which was the hypothesized control clearance rate used in

10 designing phase II of COBRA.”) By not critically assessing the COBRA data and assumptions

11 underlying its futility analysis, Dr. Hochster failed to employ the rigor demanded of an expert.

12 *Grimes v. Hoffman-LaRoche, Inc.*, 907 F. Supp. 33, 38 (D.N.H. 1995) (excluding expert whose

13 “opinion is based on an untested assumption which fails *Daubert's* reliability and fit requirements”).

14 3. COBRA’s flawed scheduling of blood draws during chemotherapy

15 COBRA’s six-month post-baseline blood draw took place *during* chemotherapy. Morris

16 Presentation slide 5 (“The 6-month timepoint was collected two weeks after prior dose of

17 chemotherapy/immediately prior to the administration of the last dose of chemotherapy.”) [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 [REDACTED]

23 [REDACTED]

24 [REDACTED]

25 [REDACTED]

26 [REDACTED]

27 [REDACTED]

28 [REDACTED]

Consistent with Guardant’s experience, current scholarship recommends ctDNA testing *after* adjuvant chemotherapy concludes. E.g., Ex. 3102, M. Malla, et al., Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices J Clin Oncol 40:2846-2857 (2022):

Ideally, MRD assessment should be before initiation of adjuvant chemotherapy and not during systemic therapy. *In the surveillance setting, assessment of ctDNA for MRD at least 2-4 weeks after completion of adjuvant therapy is reasonable.*

(emphasis added).

Hochster COBRA Dep. 130:4-131:5. Indeed, it does not appear “any unpublished data . . . validates the use of ctDNA tests for any purpose *during* adjuvant therapy.” Parikh Rebuttal Rept. ¶ 74 (noting Parikh Study measured ctDNA after adjuvant chemotherapy).

COBRA’s design failed to anticipate that blood draws should not be taken during chemotherapy, and Dr. Hochster failed to account for this flaw in offering his COBRA opinions.

4. Clinical outcome data are needed to measure COBRA false positives

1 Confoundingly, Dr. Hochster states: “Without the benefit of knowing patients’ recurrence
 2 outcomes, the COBRA study avoids the risk of biasing the results and create an ideal condition to
 3 test the performance of an assay.” *Id.* ¶ 17. [REDACTED]
 4 [REDACTED].” *Id.* at 86:10-13; *id.* at 87:17-
 5 88:8. Based on this circular definition, he concluded COBRA’s Phase II data “demonstrate that the
 6 Reveal test does not work as Guardant and Dr. Parikh reported.” Hochster Suppl. Rept. ¶ 28.

7 Relying on untested assumptions is just another word for guessing. Unlike the Parikh Study,
 8 “[e]valuating the clinical performance (i.e., the sensitivity, specificity, positive predictive value,
 9 and negative predictive value) of Reveal was *not* a stated objective of COBRA.” Heitjan Rebuttal
 10 Rept. ¶ 12; *see also* Parikh Rebuttal Rept. ¶¶ 14, 48. Rather, “[t]he phase II endpoint analysis tested
 11 the null hypothesis that the clearance rates are the same among initially ctDNA(+) subjects in both
 12 study arms.” Heitjan Rebuttal Rept. ¶ 39. The study NRG designed was unable to disprove this null
 13 hypothesis. That does not mean, however, that any of the Reveal test results in either Arm 1 or
 14 Arm 2 were “false positives”—As Dr. Hochster admits there is simply no way to make that
 15 determination without having clinical outcome data to prove the clinical truth of these results.

16 Nor is there any basis for Dr. Hochster’s renewed attack on the Parikh Study. The
 17 MGM/Harvard study “showed Reveal to be a highly specific and moderately sensitive predictor of
 18 CRC recurrence in a mixed cohort of patients with tumors of stages I, II, III, or IV.” Heitjan
 19 Rebuttal Rept. ¶ 72. By contrast, “[t]he pivotal COBRA phase II analysis, however, did not measure
 20 CRC recurrence. It considered only ctDNA clearance, a far less clinically important outcome that
 21 has not yet been validated as an adequate surrogate for evaluating therapeutic response.” *Id.* In
 22 short: “The COBRA data does not prove anything about the clinical performance of Reveal in the
 23 Parikh Study.” *Id.*; *see also* Parikh Rebuttal Rept. ¶¶ 48-50.

24 5. [REDACTED] does not prove earlier results were errors

25 [REDACTED]
 26 [REDACTED] Hochster COBRA Dep. 25:8-26:11, both Guardant and [REDACTED]
 27 [REDACTED]. Aleshin COBRA Dep. 192:20-193:5. Nevertheless,
 28 Dr. Hochster relies on Ex. H (discussing [REDACTED] [REDACTED])

Amendment ¶ 5. He goes on to

,” *id.* ¶ 6.

Reveal’s had no impact on the clinical results validated in the Parikh Study—landmark sensitivity and specificity remained 56% and 100% respectively. Ex. H; Parikh Rebuttal Rept. ¶ 68 (“the clinical specificity that we reported in the MGH/Harvard study did not change – it remained 100% for patients with at least 1 year of clinical follow up”); *accord*, Hochster COBRA Dep. 303:17-304:12.

Dr. Hochster has known since September 13, 2023, that , *see* Preliminary Abstract, which would have passed the futility analysis. *Id.*

But again, without recurrence data, there is no basis for concluding that either the original or re-run tests were true or false positives. *See* Hochster COBRA Dep. 310:9-14.

6. Dr. Hochster’s opinions about Signatera’s performance are speculative

Dr. Hochster’s opinion that “Guardant Reveal’s poor performance in the COBRA” supports his opinion that Reveal “is not on par with tumor-informed tests,” Hochster Suppl. Rept. ¶ 46, is sheer speculation. *See* Heitjan Rebuttal Rept. ¶ 75 (observing that Dr. Hochster provides no “valid basis for” this conclusion); *see also* Parikh Rebuttal Rept. ¶ 16 (“The COBRA study did not use a tumor-informed ctDNA assay in addition to Reveal. For this reason, it provides no valid scientific basis for comparing the two types of ctDNA assays, or for Dr. Hochster’s conclusion that the COBRA study shows that ‘the true performance of Reveal,’ ‘is not on par with tumor-informed tests.’”).

Indeed,

Notably, “data from the Galaxy study presented at ASCO GI 2024 and

1 attached as Exhibit 4 to Dr. Hochster's Supplemental Report shows that the specificity of the tumor-
 2 informed approach at an MRD timepoint (2-10 weeks post-surgery) was 93.6% for Stage I-IV
 3 patients (slide 4), and 92.6% for Stage II and III patients (slide 5)." Parikh Rebuttal Rept. ¶ 51.
 4 "Based on these data, we would not expect the performance of a tumor-informed test to be better
 5 than Reveal in the patient cohort addressed in COBRA." *Id.*; see also Heitjan Rebuttal Rept. ¶ 73.

6 Under *Daubert*, an expert's personal opinions are inadmissible, see *Daubert v. Merrell Dow*
 7 *Pharms., Inc.*, 43 F.3d 1311, 1315 (9th Cir. 1995), and speculation is inherently unreliable. *Diviero*
 8 *v. Uniroyal Goodrich Tire Co.*, 114 F.3d 851, 853 (9th Cir. 1997). But here, Dr. Hochster bases his
 9 opinions about COBRA on assumptions and guesswork and nothing else. They should be excluded.

10 **D. Dr. Hochster's opinions about COBRA are unduly prejudicial**

11 Expert opinion which satisfies Rule 702 may be excluded "if its probative value is
 12 substantially outweighed by a danger of . . . unfair prejudice, confusion of the issues or misleading
 13 the jury." FED. R. EVID. 403. Rule 403 plays an important role in the scrutiny of expert testimony
 14 "given the unique weight such evidence may have in a jury's deliberations." *Nimely v. City of New*
 15 *York*, 414 F.3d 381, 397 (2d Cir. 2005). Because "[e]xpert evidence can be both powerful and
 16 quite misleading," "the judge in weighing possible prejudice against probative force under Rule
 17 403 . . . exercises more control over experts than over lay witnesses." *Daubert*, 509 U.S. at 595.

18 Evidence about COBRA is at most tangentially and conditionally relevant to the questions
 19 for the jury: whether the parties' advertising in the first half of 2021 was false, misleading, and
 20 injurious to the other party. For example, the Court identified the "cap" on a damages award for
 21 prospective corrective advertising costs as one area of potential relevance for COBRA. Dkt. 493 at
 22 12. But Dr. Hochster offers no opinions on Guardant's sales of Reveal, and he admitted he does not

23 [REDACTED]

24 Nor is there other evidence COBRA dissuaded consumers from using Reveal because of
 25 the results of COBRA. Dkt. 493 at 12. In fact, the evidence shows the contrary. [REDACTED]

26 [REDACTED]
 27 [REDACTED]
 28 [REDACTED]

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[REDACTED]

But Natera's marketing efforts to capitalize on COBRA failed. In the example above, the

[REDACTED] Aleshin

COBRA Dep. 86:24-87:3. [REDACTED] *Id.* at 90:2-9.

[REDACTED]

The Court also held that aspects of COBRA potentially could be pertinent to materiality. Dkt. 493 at 9. But materiality, whether an ad influenced purchasing decisions, is “typically proven through consumer surveys.” *Clorox Co. v. Reckitt Benckiser Grp. PLC*, 398 F. Supp. 3d 623, 644 (N.D. Cal. 2019). Natera conducted no surveys, and Dr. Hochster is unqualified to opine as to the impact of COBRA on others: “As the Court previously ruled, Dr. Hochster may only report his own opinions, not the opinions of other oncologists in the field without providing a basis for his knowledge.” Dkt. 493 at 12 (holding: “Dr. Hochster’s descriptions of opinion testimony of other oncologists is inadmissible pursuant to the Court’s prior Order”) (citing Dkt. No. 328).

Finally, a discussion of COBRA inevitably will mislead and confuse the jury as a unique outlier in this case. This is not because COBRA is actually important; while Natera now insists the premature discontinuation of a study is “unprecedented,” Hochster Suppl. Rept. ¶ 8 (it is not)⁴ and “shook the field” (it did not), [REDACTED] Ex. L NATERA_234198 (Jan. 15, 2020). Rather, COBRA will be prominent because all other fact discovery ended by August 2022. Document discovery had been completed months before that. With the exception of some updated financials, Natera’s documents had been collected by January 2022. There have been many significant developments for Guardant and Reveal and Natera and Signatera since then.

But the jury is unlikely to understand—or ever know—that COBRA is the only *new* evidence being introduced, notwithstanding what at best amounts to tangential and conditional relevance, only because of Natera’s procedural maneuverings. It is virtually inevitable the jury thus will give outsized attention and weight to COBRA. This is the very definition of undue prejudice.

CONCLUSION

The Court should exclude all testimony from Dr. Hochster on COBRA.

⁴ More than a quarter of nearly nine hundred clinical trials surveyed were discontinued prematurely, “mostly due to reasons such as poor recruitment, administrative reasons, or unexpected harm.” M. Stegert *et al.*, DISCO study group An analysis of protocols and publications suggested that most discontinuations of clinical trials were not based on preplanned interim analyses or stopping rules. *J Clin Epidemiol.* 2015;69:152–60. As one example, GSK’s “ZEST” clinical trial, involving Signatera, launched in August 2021, and closed prematurely in April 2023. Moreover, about one-in-twenty clinical trials close due to futility. S.D. Walter *et al.*, A systematic survey of randomized trials that stopped early for reasons for futility, *BMC Med. Res. Methodology* (2010) 20:10 (46 of 894 surveyed trials, or 5.1%, were discontinued for early benefit or futility).

1 Dated: July 1, 2024

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5 GUARDANT HEALTH, INC.
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